

ES cell lines constitute patentable subject matter (U.S. Patents Nos. 6,207,371, 6,204,061, 5,789,215, etc.), and that genetically engineered mice constitute patentable subject matter (5,948,952, 4,736,866, etc.)— and especially, as in the present case, genetically engineered mice that define a novel modes of medical intervention. Thus, the only remaining question for the present inquiry is where and how in the above continuum of patentable scientific utility, the utility of the described ES cell line has somehow vanished?

RESPONSE

I. Status of the Claims

Claim 2 has been cancelled. Remaining Claims 1, and 3-7 are thus presently pending and stand as rejected under 35 USC §§ 101/112. No prior art rejections are presently of record. Claims 1 and 7 have been amended to address some of the issues raised by the Examiner in the Action. Support for the amended claims language can be found, *inter alia*, in the original claims as filed, and in the specification at page 4 lines 29-32. Accordingly, the amendments are not deemed to constitute new matter.

II. The Present Claims Are Patentable And The Rejections of Record Should Be Withdrawn.

a) Rejections Under 35 U.S.C. § 101 and §112, First Paragraph

The Examiner's rejections of Claims 1-7 under 35 U.S.C. section 101 and the intertwined rejections under section 112, first paragraph are respectfully traversed. The Examiner has apparently adopted the position that the claimed invention lacks patentable utility due to its not being supported by either a specific and/or substantial utility or a well established utility. Many of the Examiner's concerns about the breadth of the claims are deemed to have been avoided by amendment.

Applicants are enclosing herewith as Exhibit B, a courtesy copy of GENSEQ accession no. Y84372 as identified in Figure 2, line 2 of the instant application which shows that scientists wholly unaffiliated with the Applicants had identified the mutated gene as encoding a voltage-gated calcium channel as early as 1998), the mice exhibited marked hyperactivity. Exhibit B provides dispositive evidence of record that clearly establishes that the CACNG8 gene was indeed known at the time the present application was filed.

The use of the described ES cells (using well-established methods that are widely known in the

art, see, for example, U.S. Patent No. 6,207,371 at columns 15-16 which was incorporated by reference into the present specification) to produce animals that stably maintain the mutated form of the murine CACNG8 allele are specifically contemplated in the last paragraph of the Summary of the Invention (pages 3-4). In view of the clear hyperactivity, and thus medically relevant, phenotype attributable to the specifically exemplified ES cells, there can be no question that the described ES cell lines have a substantial and specific “real world” utility. In summary, when the described ES cells were used to produce mutant animals *as specifically contemplated in the specification*, the resulting animals had a profound and medically relevant behavioral phenotype. Given that there can be no question that the described genetically engineered animals define a patentable invention and utility, how can the ES cells used to generate the animals not have a patentable utility? From a practical standpoint, the present quandary presents a mammalian version of the age old chicken-or-the-egg paradox. In this case, it is clear that a patentable genetically engineered chicken would produce patentable eggs which would then produce patentable chickens....

Finally, the Examiner has seemed to imply that the present invention cannot have utility because the functional properties of the mutated gene were not previously known. This naturally begs the question, if the physiological function of a given sequence was actually already known, why conduct the experiment? One point worth raising here is that although the commercial utility of doing such a hypothetical experiment might be questionable, there would be little question that, according to the Examiner’s logic, the experiment would almost certainly have a patentable utility (which is somewhat illustrative of the crosswise logic/policy considerations presently guiding the broader utility debate within the field). Again, the broad failure of the scientific community to reliably predict physiological function using bioinformatics, expression data, proteomics, biochemical activity, and cell-based data has largely motivated the present scientific inquiry and invention. It is ironic that many of the technologies these deficient technologies that have proven demonstrably inferior to the described methods and compositions, have been deemed to have patentable utility by the United States Patent Office.

In view of the overwhelming evidence of the substantial, credible, specific, and well-established utility of the presently claimed invention, and in view of the absence of any evidence of record specifically refuting the utility of the described cell clones containing a genetically engineered mutation in the CACNG8 gene, the Applicants’ respectfully request that the Examiner withdraw the pending rejection of Claims 1, and 3-7 under 35 U.S.C. section 101 as well as the related rejections under 35 U.S.C. section 112, first paragraph.

b) Additional Rejections under 35 U.S.C. Section 112, First Paragraph

The Examiner has also rejected the Claims under 35 U.S.C. section 112, first paragraph for allegedly failing to comply with the written description requirement. As discussed in a prior response, those skilled in the art would understand that in order to generate the exon sequence data described in the specification and Sequence Listing, the Applicants must be in actual possession of the described ES cell clones. Thus, there can be no scientifically credible assertion that the Applicants were not in ACTUAL POSSESSION of the claimed invention. To the extent that the Examiner still remains unpersuaded, Applicants can deposit the ES cell lines at issue with the ATCC to dispositively deal with the written description issue when and if all other remaining issues of patentability have been resolved.

In view of the above remarks and considerations, the Examiner is respectfully requested to withdraw the pending rejection of Claims 1, and 2-7 under 35 U.S.C. §112, first paragraph for alleged want of adequate written description..

To the extent that the Examiner might suggest alternative claims language that would avoid any of the above rejections, the Examiner is invited to suggest such language if it will put the claim or claims in condition for allowance.

III. CONCLUSION

In view of the foregoing amendments and remarks, the Applicants believe that the application is in good and proper condition for allowance. Early notification to that effect is earnestly solicited.

If the Examiner feels that a telephone call would expedite the consideration of the application, the Examiner is invited to call the undersigned attorney at (281) 863-3333. The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-0892 for any matter in connection with this response, including fees for any extension of time, which may be required.

Respectfully submitted,



Lance K. Ishimoto
Attorney for Applicant

Reg. No. 41,866

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Date

Customer # 24231

LEXICON GENETICS INCORPORATED
8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3333

The Knockout Mouse Project

Mouse knockout technology provides a powerful means of elucidating gene function *in vivo*, and a publicly available genome-wide collection of mouse knockouts would be significantly enabling for biomedical discovery. To date, published knockouts exist for only about 10% of mouse genes. Furthermore, many of these are limited in utility because they have not been made or phenotyped in standardized ways, and many are not freely available to researchers. It is time to harness new technologies and efficiencies of production to mount a high-throughput international effort to produce and phenotype knockouts for all mouse genes, and place these resources into the public domain.

Now that the human and mouse genome sequences are known¹⁻³, attention has turned to elucidating gene function and identifying gene products that might have therapeutic value. The laboratory mouse (*Mus musculus*) has had a prominent role in the study of human disease mechanisms throughout the rich, 100-year history of classical mouse genetics, exemplified by the lessons learned from naturally occurring mutants such as agouti⁴, reeler⁵ and obese⁶. The large-scale production and analysis of induced genetic mutations in worms, flies, zebrafish and mice have greatly accelerated the understanding of gene function in these organisms. Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.

The ability to disrupt, or knock out, a specific gene in ES cells and mice was developed in the late 1980s (ref. 7), and the use of knockout mice has led to many insights into human biology and disease⁸⁻¹¹. Current technology also permits insertion of 'reporter' genes into the knocked-out gene, which can then be used to determine the temporal and spatial

expression pattern of the knocked-out gene in mouse tissues. Such marking of cells by a reporter gene facilitates the identification of new cell types according to their gene expression patterns and allows further characterization of marked tissues and single cells.

Appreciation of the power of mouse genetics to inform the study of mammalian physiology and disease, coupled with the advent of the mouse genome sequence and the ease of producing mutated alleles, has catalyzed public and private sector initiatives to produce mouse mutants on a large scale, with the goal of eventually knocking out a substantial portion of the mouse genome^{12,13}. Large-scale, publicly funded gene-trap programs have been initiated in several countries, with the International Gene Trap Consortium coordinating certain efforts and resources¹⁴⁻¹⁷.

Despite these efforts, the total number of knockout mice described in the literature is relatively modest, corresponding to only ~10% of the ~25,000 mouse genes. The curated Mouse Knockout & Mutation Database lists 2,669 unique genes (C. Rathbone, personal communication), the curated Mouse Genome Database lists 2,847 unique genes, and an analysis at Lexicon Genetics identified 2,492 unique genes (B.Z., unpublished data). Most of these knockouts are not readily available to scientists who may want to use them in their research; for example, only 415 unique genes are represented as targeted mutations in the Jackson Laboratory's Induced Mutant Resource database (S. Rockwood, personal communication).

The converging interests of multiple members of the genomics community led to a meeting to discuss the advisability and feasibility of

a dedicated project to produce knockout alleles for all mouse genes and place them into the public domain. The meeting took place from 30 September to 1 October 2003 at the Banbury Conference Center at Cold Spring Harbor Laboratory. The attendees of the meeting are the authors of this paper.

Is a systematic project warranted?

A coordinated project to systematically knock out all mouse genes is likely to be of enormous benefit to the research community, given the demonstrated power of knockout mice to elucidate gene function, the frequency of unpredicted phenotypes in knockout mice, the potential economies of scale in an organized and carefully planned project, and the high cost and lack of availability of knockout mice being made in current efforts. Moreover, implementing such a systematic and comprehensive plan will greatly accelerate the translation of genome sequences into biological insights. Knockout ES cells and mice currently available from the public and private sectors should be incorporated into the genome-wide initiative as much as possible, although some may be needed to be produced again if they were made with suboptimal methods (e.g., not including a marker) or if their use is restricted by intellectual property or other constraints. The advantages of such a systematic and coordinated effort include efficient production with reduced costs; uniform use of knockout methods, allowing for more comparability between knockout mice; and ready access to mice, their derivatives and data to all researchers without encumbrance. Solutions to the logistical, organizational and informatics issues associated with producing, characterizing and distributing such a large number of

*The Comprehensive Knockout Mouse Project Consortium**

**Authors and their affiliations are listed at the end of the paper.*

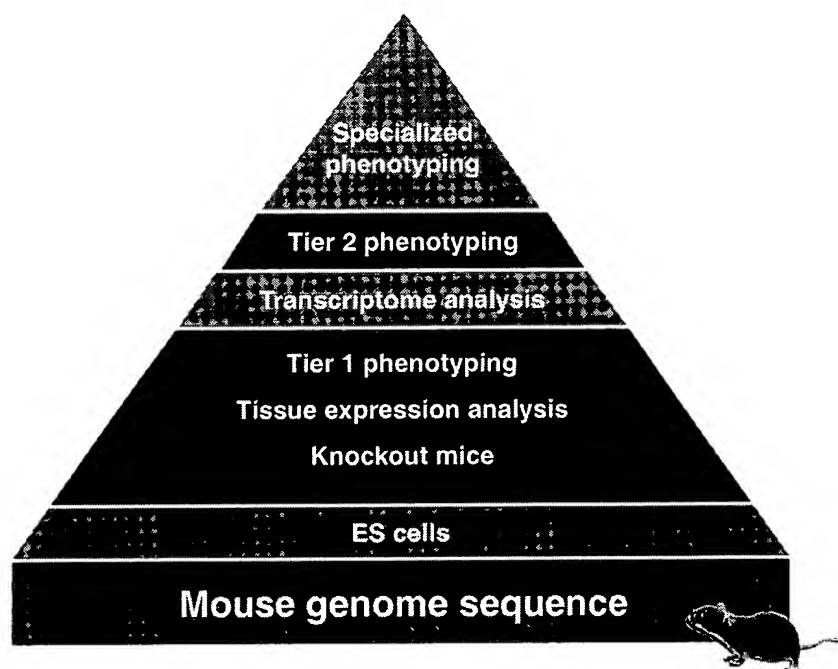


Figure 1 Structure of resource production in the proposed KOMP. Using the mouse genome sequence as a foundation, knockout alleles in ES cells will be produced for all genes. A subset of ES cell knockouts will be used each year to produce knockout mice, determine the expression pattern of the targeted gene in a variety of tissues and carry out screening-level (Tier 1) phenotyping. In a subset of mouse lines, transcriptome analysis and more detailed system-specific (Tier 2) phenotyping will be done. Finally, specialized phenotyping will be done on a smaller number of mouse lines with particularly interesting phenotypes. All stages will occur within the purview of the KOMP except for the specialized phenotyping, which will occur in individual laboratories with particular expertise.

mice will draw from the experience of related projects in the private sector and in academia, which have made or phenotyped hundreds of knockout mice using a variety of techniques. Lessons learned from these projects include the need for redundancy at each step to mitigate pipeline bottlenecks and the need for robust informatics systems to track the production, analysis, maintenance and distribution of thousands of targeting constructs, ES cells and mice.

Null-reporter alleles should be created

The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., β -galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene. Therefore, we propose to produce a null-reporter allele for each gene. Making each mutation conditional in nature by adding *cis*-elements (e.g., *loxP* or FRT sites) would

be desirable, but we do not advocate this as part of the mutagenesis strategy unless the technological limitations currently associated with generating conditional targeted mutations on a large scale and in a cost-effective manner can be overcome.

A combination of methods should be used

Various methods can be used to create mutated alleles, including gene targeting, gene trapping and RNA interference. Advantages of conventional gene targeting include flexibility in design of alleles, lack of limitation to integration hot spots, reliability for producing complete loss-of-function alleles, ability to produce reporter knock-ins and conditional alleles, and ability to target splice variants and alternative promoters. BAC-based targeting has the potential advantages of higher recombination efficiencies and flexibility for producing complex mutated alleles¹⁸. Gene trapping is rapid, is cost-effective and produces a large variety of insertional mutations throughout the genome but can be somewhat less flexible^{17,19–21}. There is uncertainty regarding the percentage of gene traps that produce a true null allele and the fraction

of the genome that can ultimately be covered by gene-trap mutations. Trapping is not entirely random but shows preference for larger transcription units and genes more highly expressed in ES cells. In recent studies, gene trapping was estimated to potentially produce null alleles for 50–60% of all genes, perhaps more if a variety of gene-trap vectors with different insertion characteristics is used^{17,21}. RNA interference offers enormous promise for analysis of gene function in mice²² but is not yet sufficiently developed for large-scale production of gene modifications capable of reliably producing true null alleles. Both gene-targeting and gene-trapping methods are suitable for producing large numbers of knockout alleles, and, given their complementary advantages, a combination of these methods should be used to produce the genome-wide collection of null-reporter alleles most efficiently.

What should the deliverables be?

A genome-wide knockout mouse project could deliver to the research community a trove of valuable reagents and data, including targeting and trapping constructs and vectors, mutant ES cell lines, live mice, frozen sperm, frozen embryos, phenotypic data at a variety of levels and detail, and a database with data visualization and mining tools. At a minimum, we believe that a comprehensive genome-wide resource of mutant ES cell lines from an inbred strain, each with a different gene knocked out, should be produced and made available to the community. Choosing an inbred line (129/SvEvTac or C57BL/6J), and evaluating the alternative of using F₁ ES cells and tetraploid aggregation to provide potential time savings, merits additional scientific review and discussion^{23,24}. ES cells should be converted into mice at a rate consistent with project funding and the ability of the worldwide scientific community to analyze them. Although the value and cost-effectiveness of systematically characterizing the mice is a matter of debate, a limited set of broad and cost-effective screens, probably including assessment of developmental lethality, physical examination, basic blood tests, and histochemical analysis of reporter gene expression, would be useful. More detailed phenotyping, based on findings from the initial screen or existing knowledge of the gene's function, could be done at specialized centers. All ES cell clones and mice (as frozen embryos or sperm) should be available to any researcher at minimal cost, and all mouse phenotyping and reporter expression data should be deposited into a public database.

In determining how to implement the project, utility to the research community should be the standard for judging value. Each step after ES cell generation (e.g., mouse creation, breeding, expression analysis, phenotyping) will make the resource useful to more researchers but will also increase costs and scientific complexity. We therefore advocate a 'pyramid' structure for the project (Fig. 1). At the base of the pyramid is the genome-wide collection of mutant ES cells for every mouse gene. Over time, a subset of these mutant ES cells should be made into mice and characterized with an initial phenotype screen (Tier 1; Fig. 1) and analysis of tissue reporter-gene expression. A subset of these lines should be profiled by microarray analysis, and a subset of these profiled by system-specific (Tier 2) phenotyping, based on the results of the Tier 1 phenotyping, array studies, existing knowledge of the gene's function and the gene's tissue expression pattern. With time, the upper tiers of the pyramid will be filled out, eventually transforming the pyramid into a cube, with information of all types available for all genes.

This project will require the resolution of numerous intellectual property claims involving the production and use of knockout mice. To deal with the existing patents that cover the technologies and processes involved in the production of mutant mice, we suggest that a 'patent pool', such as that used in the semiconductor industry²⁵, should be generated. Several individuals who represent entities that control patents on mouse knockout technologies are authors on this paper, and they agree with this approach. We also agree that any mutant ES cells or mice produced should be placed immediately in the public domain.

Mechanisms and costs

ES cell production. Automated knockout construct and ES cell production should be carried out in coordinated centers to ensure efficiency and uniformity. We estimate that most known mouse genes could be knocked out in ES cells within 5 years, using a combination of gene-trapping and gene-targeting techniques. Gene trapping can produce a large number of mutated alleles quickly, but its progress should be monitored closely to determine when its yield of new genes diminishes¹⁷ and, therefore, when targeting should be increasingly relied on. As large-scale trapping projects have already defined gene classes that probably cannot be knocked out by trapping (e.g., single-exon GPCRs, genes that are not expressed in ES cells), we propose that targeting begin on those classes immediately. All ES cells should be made available to the research community, because this collection itself

would be a valuable resource. Efforts in the public and private sectors have already knocked out many genes in ES cells, and, to the degree that the alleles produced fit the prescribed characteristics (i.e., null alleles with a reporter) and are available, every effort should be made to incorporate these into the planned public resource. Costs for generating this part of the resource were estimated at between \$9–11 million/year for five years (these and all subsequent figures are direct costs).

Mouse production. The subset of ES cells made into mice each year should be chosen by a peer-review process. Central facilities for high-efficiency mouse production, genotyping, breeding, maintenance and archiving should be funded, to take advantage of efficiencies of scale in mouse creation and distribution. Researchers could apply to produce groups of mice outside the centers, as long as they meet the cost specifications of the program. All mice should be made available immediately to researchers as frozen embryos or sperm, for nominal distribution cost. An initial target of 500 new mouse lines per year would double the current rate at which new genes are knocked out in the public sector; we feel that this rate is within the capacity of the biomedical research community worldwide to absorb and analyze. We estimated the initial cost of this level of mouse production to be \$12.5–15 million per year.

Reporter tissue expression analysis. Approximately 30 tissues from adult and developmental stages should be sampled to cover the main organ systems. Analysis methods should be customized to the organ system and marker, and a searchable database of the sites of gene expression, and the images showing them, should be produced. Centers to carry out these analyses and data curation should be selected by peer review. We estimated the cost of this component for 500 mouse lines to be \$2.5–5 million per year, depending on how much tissue sectioning and cell-level analysis is done.

Phenotyping. Tier 1 phenotyping should be a low-cost screen for clear phenotypes and should be done on all mouse lines produced. Tier 1 should include home-cage observation, physical examination, blood hematological and chemistry profiles, and skeletal radiographs. The centers producing the mice should carry out the Tier 1 analyses, at an estimated cost of \$2.5 million per year for 500 lines. Selected lines, chosen on the basis of findings from Tier 1 phenotyping, tissue expression patterns, microarray data and the scientific literature, should undergo more detailed and system-focused Tier 2 phenotyping. Tier 2 phenotyping should be done in

specialized phenotyping centers, akin to those already in operation for phenotyping of mice produced by ENU mutagenesis. All Tier 1 and Tier 2 phenotyping should be done on a uniform genetic background by dedicated groups of individuals in single locations, to facilitate consistency and cross-comparison of results among different mouse lines. All Tier 1 and Tier 2 phenotyping results should be deposited into a central project database freely accessible to the research community. More detailed and specialized phenotyping could be done by individual researchers in their own laboratories; deposition of this more detailed phenotype data would be encouraged.

Transcriptome analysis. Transcriptome profiling of tissues from each knockout line, collected in a uniform way across all mice and tissues and placed into a searchable relational database, would add substantially to the scientific value of the project, though it would also add considerably to its cost. Transcriptome analysis should therefore be done on a subset of mice, chosen by peer review. We estimate that, with the best currently available array technology, an analysis of ten tissues would cost ~\$18,000 per line.

Conclusions

This project, tentatively named the Knockout Mouse Project (KOMP), will be a crucial step in harnessing the power of the genome to drive biomedical discovery. By creating a publicly available resource of knockout mice and phenotypic data, KOMP will knock down barriers for biologists to use mouse genetics in their research. The scientific consensus that we achieved—that a dedicated project should be undertaken to produce mutant mice for all genes and place them into the public domain—is important but is only the beginning. Implementation of these recommendations will require additional input from the greater scientific community, including those responsible for programmatic direction and financial support of biomedical research in the public and private sectors. This ambitious and historic initiative must be carried out as a collaborative effort of the worldwide scientific community, so that all can contribute their skills, and all can benefit. International discussions among scientific and programmatic staffs since the Banbury meeting at Cold Spring Harbor, in both the public and private sectors, have shown that there is great enthusiasm and commitment to this vision. The next step for KOMP will be to move this visionary plan from conceptualization to implementation, with an urgency befitting the benefits it will bring to science and medicine.

COMMENTARY

URLs. The curated Mouse Knockout & Mutation Database is available at <http://research.bmn.com/mkmd/>. The curated Mouse Genome Database is available at <http://www.informatics.jax.org/>. *Patent pools: A solution to the problem of access in biotechnology patents?* is available at <http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf>.

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Christopher P Austin¹, James F Battey², Allan Bradley³, Maja Bucan⁴, Mario Capecchi⁵, Francis S Collins⁶, William F Dove⁷, Geoffrey Duyk⁸, Susan Dymecki⁹, Janan T Eppig¹⁰, Franziska B Grieder¹¹, Nathaniel Heintz¹², Geoff Hicks¹³, Thomas R Insel¹⁴, Alexandra Joyner¹⁵, Beverly H Koller¹⁶, K C Kent Lloyd¹⁷, Terry Magnuson¹⁸, Mark W Moore¹⁹, Andras Nagy²⁰, Jonathan D Pollock²¹, Allen D Roses²², Arthur T Sands²³, Brian Seed²⁴, William C Skarnes²⁵, Jay Snoddy²⁶, Philippe Soriano²⁷, David J Stewart²⁸, Francis Stewart²⁹, Bruce Stillman²⁸, Harold Varmus³⁰, Lyuba Varticovski³¹, Inder M Verma³², Thomas F Vogt³³, Harald von Melchner³⁴, Jan Witkowski³⁵, Richard P Woychik³⁶, Wolfgang Wurst³⁷, George D Yancopoulos³⁸, Stephen G Young³⁹ & Brian Zambrowicz⁴⁰

¹National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, 31 Center Drive, Bethesda, Maryland 20892, USA. ²National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Building 31, Room 3C02, Bethesda, Maryland 20892, USA. ³The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK. ⁴Department of Genetics, University of Pennsylvania, 111 Clinical Research Building, 415 Curie Boulevard, Philadelphia, Pennsylvania 19104-6145, USA. ⁵University of Utah, Eccles Institute of Human Genetics, Suite 5400, Salt Lake City, Utah 85112, USA. ⁶National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, 31 Center Drive, Bethesda, Maryland 20892, USA. ⁷McArdle Laboratory for Cancer Research, University of Wisconsin - Madison, 1400 University Avenue, Madison, Wisconsin 53706-1599, USA. ⁸TPG Ventures, 345 California Street, Suite 2600, San Francisco, California 94104, USA. ⁹Harvard Medical School, Department of Genetics, 77 Avenue Louis Pasteur, Boston, Massachusetts 02115, USA. ¹⁰The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine 04609-1500, USA. ¹¹National Center for Research Resources, National Institutes of Health, 1 Democracy Plaza, 6701 Democracy Boulevard, Bethesda, Maryland 20817-4874, USA. ¹²Laboratory of Molecular Biology, The Rockefeller University, 1230 York Avenue, New York, New York 10021, USA. ¹³Manitoba Institute of Cell Biology, 675 McDermot Avenue, Room ON5029, Winnipeg, Manitoba R3E 0V9, Canada. ¹⁴National Institute of Mental Health, 6001 Executive Blvd. - Rm 8235- MSC 9669, Bethesda, Maryland 20892-9669, USA. ¹⁵Skirball Institute of Biomolecular Medicine, 540 First Avenue, 4th Floor, New York, New York 10016, USA. ¹⁶Department of Genetics, University of North Carolina, CB 7248, 7007 Thurston Bowles Bldg, Chapel Hill, North Carolina 27599, USA. ¹⁷School of Veterinary Medicine, University of California, One Shields Avenue, Davis, California 95616, USA. ¹⁸Department of Genetics, Room 4109D Neurosciences Research Building, University of North Carolina, CB 7264, 103 Mason Farm Road, Chapel Hill, North Carolina 27599, USA. ¹⁹Deltagen, 740 Bay Road, Redwood City, California 94063-2469, USA. ²⁰Samuel Lunenfeld Research Institute, University of Toronto, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada. ²¹National Institute on Drug Abuse, 6001 Executive Blvd, Rm 4274, Bethesda, Maryland 20892, USA. ²²GlaxoSmithKline, 5 Moore Drive, Durham, North Carolina 27709, USA. ²³Lexicon Genetics, 8800 Technology Forest Place, The Woodlands, Texas 77381-1160, USA. ²⁴Department of Molecular Biology, Massachusetts General Hospital, Wellman 911, 55 Fruit Street, Boston, Massachusetts 02114, USA. ²⁵The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK. ²⁶The University of Tennessee-ORNL Graduate School of Genome Science and Technology, PO Box 2008, MS6164, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37831-6164, USA. ²⁷Division of Basic Sciences, A2-025, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, P.O. Box 19024, Seattle, Washington 98109-1024, USA. ²⁸Cold Spring Harbor Laboratory, 1 Bungtown Road, PO Box 100, Cold Spring Harbor, New York 11724, USA. ²⁹Bioz, University of Technology, Dresden, c/o MPI-CBG, Pfotenhauerstr 108, 1307 Dresden, Germany. ³⁰Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021, USA. ³¹National Cancer Institute, National Institutes of Health, 31 Center Drive, Room 3A11, Bethesda, Maryland 20892-2440, USA. ³²Molecular Biology and Virology Laboratory, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037-1099, USA. ³³Merck Research Laboratories, PO Box 4, WP26-265, 770 Sumneytown Pike, West Point, Pennsylvania 19486, USA. ³⁴Laboratory for Molecular Hematology, University of Frankfurt Medical School, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany. ³⁵Banbury Center, Cold Spring Harbor Laboratory, PO Box 534, Cold Spring Harbor, New York 11724-0534, USA. ³⁶The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine 04609, USA. ³⁷Institute of Developmental Genetics, GSF Research Center, Max-Planck-Institute of Psychiatry, Ingolstaeder Landstr. 1, 85764 Munich/Neuherberg, Germany. ³⁸Regeneron Pharmaceuticals, 777 Old Saw Mill River Road, Tarrytown, New York 10591, USA. ³⁹Gladstone Foundation for Cardiovascular Disease, University of California, San Francisco, California, USA. ⁴⁰Lexicon Genetics, 8800 Technology Forest Place, The Woodlands, Texas 77381-1160, USA. Correspondence should be addressed to C.P.A. (austinc@mail.nih.gov).

ID AAY84372 standard; protein; 327 AA.
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AC AAY84372;
XX
DT 12-JUL-2000 (first entry)
XX
DE A human voltage-gated calcium channel designated CACNGLIKE3.
XX
KW Human; skeletal muscle; voltage-gated calcium channel; CACNGLIKE3;
KW neurological disorder; epilepsy; stroke; head trauma; migraine;
KW affective disorder; depression; anxiety; schizophrenia; pain; cancer;
KW neurodegenerative disorder; Alzheimer's disease; cognitive disorder;
KW chromosome localisation.
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OS Homo sapiens.
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PN WO200014224-A1.
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PD 16-MAR-2000.
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PF 06-SEP-1999; 99WO-GB002944.
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PR 08-SEP-1998; 98GB-00019592.
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PA (SMIK) SMITHKLINE BEECHAM PLC.
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PI Duckworth DM, Hayes PD;
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DR WPI; 2000-256976/22.
DR N-PSDB; AAZ99791.
XX
PT Isolated voltage-gated calcium channel polypeptide, designated
PT CACNGLIKE3, to treat diseases such as neurological disorders, epilepsy,
PT neurodegenerative disorders, cognitive disorders and cancer; comprises
PT 327 amino acid sequence.
XX
PS Claim 2; Page 32-33; 37pp; English.
XX
CC The present sequence represents a human skeletal muscle voltage-gated
CC calcium channel polypeptide, designated CACNGLIKE3. The CACNGLIKE3
CC polypeptide and polynucleotide are useful in the treatment of diseases
CC such as neurological disorders, epilepsy, stroke, head trauma, migraine,
CC affective disorders including depression and anxiety, schizophrenia,
CC neurodegenerative disorders including Alzheimer's disease, cognitive
CC disorders, types of pain and cancer. The polynucleotide is also valuable
CC for chromosome localisation studies. The CACNGLIKE3 polypeptide and
CC polynucleotide are also useful in diagnostic assays for detecting
CC diseases associated with inappropriate CACNGLIKE3 activity or levels
XX
SQ Sequence 327 AA;
SQ 23 A; 26 R; 13 N; 17 D; 0 B; 6 C; 5 Q; 13 E; 0 Z; 24 G; 8 H;
SQ 23 I; 30 L; 13 K; 9 M; 15 F; 14 P; 36 S; 17 T; 3 W; 16 Y; 16 V;
SQ 0 Others;

mvr cdrqlqm llttagafaa fslmaiaigt dywlyssahi cngtnltmdd gppprargd 60
lthsglwrv ciegikghc frinhfpedn dydhsseyl lrivrassvf pilstllll 120
gglcigagri yrknnivls agilfvaagl sniigiivyi ssntgdpsdk rdedkknhyn 180
ygwsfyfgal sfivaetvgv lavniyekn kelrfktkre flkasssspy armpsyryrr 240
rrsrssrst easpsrdvsp mglkitgaip mgelsmytlis replkvttaa syspdqearf 300
lqvhdffqqd lkeghvsml nrrttpv 327

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